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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/047,608	01/14/2002	Leonard Bell	59	5748

7590 01/16/2004

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EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/047,608	BELL, LEONARD	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *14-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *01102003*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application claims the benefit of the filing date of provisional application 60/262,540.

Claims 1-26 are currently pending.

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-13, drawn to a method of prophylaxis against myocardial infarction in a subject, in the Response filed October 16, 2003 is acknowledged. The traversal is on the ground(s) that the classification system of the United States Patent and Trademark Office is not conclusive proof of divisibility, the entire application must be examined as a whole when there would not be a serious burden on the Examiner, and the fields of search are believed to be co-extensive for the two groups identified by the Examiner. This is not found persuasive because of the reasons previously stated. The practice of the invention of Group I requires the administration of "an effective myocardial infarction reducing amount" of a compound to the patient. Accordingly, the method requires the use of a compound that is known to have an effective amount. However, the method of Group II elucidates only whether a particular anti-inflammatory compound may have an effective amount. Therefore, the compounds used in the method of Group II may not be useful for Group I.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims **14-26 are withdrawn** from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the Paper filed October 16, 2003.

3. Accordingly, claims **1-13 are the subject of examination** in the present Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification

in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are most broadly drawn to the specific prophylactic treatment of a patient undergoing a cardiopulmonary bypass procedure wherein the patient has a creatine kinase with muscle and brain subunits (CK-MB) level of greater than about 50 ng/ml [claim 1], 60 ng/ml [3] 70 ng/ml [4], 80 ng/ml [5], 90 ng/ml [6], 100 ng/ml [7] or 120 ng/ml [8]. The method recites the administration of an effective myocardial infarction reducing amount of an anti-inflammatory compound in conjunction with the bypass procedure. The specification is not enabling for the claimed invention because there is no disclosure of the identification of the subject group of patients prior to the administration of an anti-inflammatory agent and the separation of those subjects from patients below the respective claimed thresholds prior to anti-inflammatory compound administration or operative procedures. The specification discloses, "no method of detecting and/or differentiating inflammatory damage from traumatic damage in patients having undergone CABG involving CPB based on postoperative CK-MB peak levels in the blood exists in the art" (page 3, lines 19-21 in particular; emphasis added for clarity). Further, the lone working example disclosed in the specification recites, [f]or purposes of CK-MB measurements, intra- and post-operative blood draws were performed at 4, 8, 16, 20, 24, 30 and 36 hours post-CBP" (page 9, lines 11-18 for example). Therefore the threshold levels of CK-MB disclosed in the specification and recited in the claims are based solely on post-operative levels of CK-MB which were not known prior to administration of an effective myocardial infarction reducing amount of an anti-inflammatory compound and therefore could not be used pre-operatively to select the patient pool which satisfies the metes and bounds of the claim. Instead, the levels determined post-operatively are used to separate the groups according to particular CK-MB thresholds based upon the reduction of the incidence of myocardial infarction in the anti-inflammatory compound-treated group *versus* sham-treated controls at the same CK-MB threshold level. Further, it is unclear that a meaningful determination of CK-MB could be made preoperatively to lower the incidence of myocardial infarction based upon a threshold level of CK-MB. Fitch (cited on form PTO-1449; Circulation (1999) 100:2499-2506) discloses that CBP induces a systemic inflammatory response that causes substantial clinical morbidity and that activation of complement during CBP contributes significantly to the inflammatory process. Bochenek (U on form PTO-892; Kardiologia Polska 36(2):67-72 (Abstract only)) discloses that complement activation results from blood contact with artificial surfaces during CBP and C3a anaphylotoxin is increased. Yilmaz (V on form PTO-892; Perfusion, (1999 May) 14 (3) 201-6) discloses that systemic inflammatory response, characterized by the activation of the known inflammatory cytokines interleukin-6 (IL-6) and interleukin-8 (IL-8), to

cardiopulmonary bypass surgery is well documented (Abstract in particular) and that CK-MB is significantly elevated in placebo treated patients after surgery (Abstract and Figure 2 in particular). Wei (W on form PTO-892; Scandinavian Journal Of Clinical And Laboratory Investigation. (2001 Apr) 61(2):161-166) discloses that postoperative CK-MB levels are significantly higher in the CPB than in auto-oxygenated controls and that elevation of cytokine levels, including IL-6 and IL-8, correlated with CK-MB (Abstract in particular). Accordingly, levels of CK-MB are largely associated with the inflammatory response to CBP. Given the limited working examples and the lack of a means in the present specification to preoperatively determine which subjects will reach a certain threshold level of CK-MB post-operatively, the artisan would not be able to predict which patients would be above the threshold level and therefore could not select a patient treatment group for anti-inflammatory administration based on the criterion of CK-MB threshold levels.

In view of the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the nature of the claimed invention, it would take undue trials and errors to practice the claimed invention and the statute does not sanction this.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Fitch et al. (cited on form PTO-1449; Circulation (1999) 100:2499-2506).

Fitch teaches the administration of a humanized single chain monoclonal antibody directed to human complement component C5 (h5G1.1-scFv) to subjects undergoing coronary bypass surgery (CBP). Fitch teaches that a post-operative measurement of CK-MB yields information on myocardial injury and that antibody-treated patients have lower CK-MB levels than placebo-treated controls (Figure 4 in particular). Fitch teaches that "[e]levated postoperative CK-MB levels are associated with an increasing incidence of postoperative ventricular regional wall abnormalities and decreased global left ventricular fraction in the early post-CABG period, which can persist up to 9 months" (page 2504, paragraph bridging columns in particular). While Fitch states that, "there does not appear to be a threshold effect," Fitch asserts that, "it is apparent that the greater the release of CK-MB, the greater the subsequent morbidity, cost, and mortality" and that, "it is likely that significant reductions in postoperative

myocardial injury might be associated with improved outcomes" (page 2504, paragraph bridging columns in particular). It is noted that Fitch is silent about patient samples comprising at least 50 ng/ml of CK-MB postoperatively, however Fitch measures CK-MB in units of IU/ml rather than in the ng/ml format used in the instant specification (Figure 4 for example). The office does not have the facilities and resources to provide the factual evidence needed in order to establish the relationship between IU and ng per ml or that there is a difference between the materials, i.e., that the claims are directed to new materials and that such a difference would have been considered unexpected by one of ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious. In the absence of evidence to the contrary, the burden is on the Applicant to prove that the claimed materials are different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). The patient groups of Fitch were randomly assigned to receive placebo or h5G1.1-scFv and therefore each group was as likely as the next to comprise patients above the "threshold" of at least about 50 ng/ml [claim 1], 60 ng/ml [3] 70 ng/ml [4], 80 ng/ml [5], 90 ng/ml [6], 100 ng/ml [7] or 120 ng/ml [8]. The results of Fitch show that all patients benefited from treatment with h5G1.1-scFv, as the level of myocardial damage, as evidenced by the level of CK-MB in the serum of antibody-treated patients was significantly lower than in the serum of placebo-treated patients (Figure 4 in particular) as supported by the assertion that, "it is likely that significant reductions in postoperative myocardial injury might be associated with improved outcomes" (page 2504, paragraph bridging columns in particular). While Fitch did not select patients preoperatively based upon a postoperative CK-MB level of at least about 50 ng/ml [claim 1], 60 ng/ml [3] 70 ng/ml [4], 80 ng/ml [5], 90 ng/ml [6], 100 ng/ml [7] or 120 ng/ml [8], it is noted that the instant specification does not provide a means for predicting postoperative CK-MB levels preoperatively. Accordingly, in the absence of evidence to the contrary, the instant invention includes the treatment of patients below a postoperative threshold level as well as those above the threshold and is therefore no different in practice than the method of Fitch. The prior art teaching anticipates the claimed invention.

Conclusion

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571)272-0852. The examiner can normally be reached on M-Th 6:30-4:00; Alternate Fridays 6:30-3:00. If attempts to reach the examiner

by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (571) 272-0841.Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
January 9, 2004

PATRICK J. NOLAN, PH.D.
PRIMARY EXAMINER
1/12/04